REMARKS

Claims 169-184 have been added to claim additional embodiments disclosed in the application as filed. The new claims are supported by the specification and original claims as filed. More specifically, support for new claims 169-184 can be found, for example, in original claims 129, 134, 139, and 144. Claims 1-124 and 145-168 have been canceled herein or previously without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to the canceled subject matter. Upon entry of the present amendment, claims 125-144 and 169-184 will be pending. No new matter has been added.

I. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 129, 134, 139 and 144

Claims 129, 134, 139 and 144 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite because "claims 129, 134, 139, and 144 are confusing in the recitation of 'including movement...including sleep...including temperature...including schizophrenia...'". *See* Office Action, page 2, third paragraph.

In response, Applicants have amended claims 129, 134, 139, and 144 to remove the references to specific group members of the disorders listed in the claims. More specifically, Applicants point out that the specific group members previously disclosed in claims 129, 134, 139, and 144 are now being pursued in dependent claims 169-184. Accordingly, Applicants submit that the rejection of claims 129, 134, 139, and 144 under 35 U.S.C. §112, first paragraph has been rendered moot.

Claim 140

Claim 140 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite because "the recitation of 'said nucleic acid' in line 3...has no antecedent basis." *See* Office Action, page 3, fourth paragraph.

In response, Claim 140 has been amended to refer to "a level of said polypeptide in said sample," which, as a result, establishes proper antecedent basis in the claim. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claim 140 under 35 U.S.C. §112, second paragraph.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 125-144 are rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement. *See* Office Action, page 2, last paragraph. Specifically, the Examiner

alleges that "there is nothing in the instant specification that teaches that any level of increase or decrease in SEQ ID NO:1 or 2 causes a disorder." *Id.* at 3 (emphasis in original).

Preliminarily, Applicants have amended claims 125 and 130 such that the claims are now directed to a method of detecting a mutated hChaT nucleic acid in a patient sample, wherein the detection of a mutated hChaT nucleic acid that differs from the hChaT nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or the hChaT cDNA contained in Deposit No. 75856 indicates that said patient has a disorder. Support for the amendments to claims 125 and 130 can be found in the specification and claims as originally filed. More specifically, support can be found, for example, on page 18, paragraph 0087.

With respect to the rejection of claims 126-129 and 131-144 and to the extent that the rejection may be applied to currently amended claims 125 and 130 and new claims 169-184, Applicants respectfully disagree and traverse. Applicants respectfully point out that the enablement requirement of 35 U.S.C. § 112, first paragraph requires nothing more than objective enablement. A specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of § 112, unless there is reason to doubt the objective truth or accuracy of the statements relied upon therein for enabling support. *Staehelin v Secher*, 24 USPQ2d 1513, 1516 (B.P.A.I. 1992), *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971); *In re Brana* 34 USPQ2d 1437, 1441 (Fed. Cir. 1995).

In order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to practice the claimed methods without "undue experimentation." Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F.2d 1386, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). In determining enablement without undue experimentation the court considers many factors. Important in these factors is the amount of guidance provided in the specification and the level of skill and knowledge in the particular art. Applicants assert that given the teachings of the specification and the level of one of skill in the art at the time the present application was filed, it cannot be said that the invention as claimed is not enabled.

Initially, Applicants note that the claims of the present invention are directed to methods of diagnosing disorders involving nucleic acids and polypeptides of human

choline acetyltransferase (hChaT). In this capacity, the specification discloses that hChaT is an enzyme that is specifically expressed in cholinergic neurons and is responsible for catalyzing a reaction, which yields the neurotransmitter acetylcholine. *See*, Specification page 1, paragraph 0003. Specifically, hChaT catalyzes the transfer of the acyl-group of acetylCoA to choline to yield acetylcholine. *Id.* at page 13, paragraph 0064. Accordingly, any decrease in the ability of hChaT to catalyze the synthesis of acetylcholine may lead to a deficiency of the neurotransmitter acetylcholine.

Deficiencies in the neurotransmitter acetylcholine are known to result in cognitive and/or neurological deficiencies and/or mood or mental disturbances, such as suffering from degenerative nervous system disorders. *Id.* Moreover, the hChaT protein has been identified as a specific marker of the cholinergic system. The cholinergic system is a series of paths in the brain and spinal cord, which are responsible for the control of movement. Disorders known to involve the cholinergic system include amyotrophic lateral sclerosis (ALS), Alzheimer's disease, senile-dementia, multi-infarct dementia, familial disautonomia, Huntington's disease, mental retardation, memory loss, and myasthenia gravis.

Therefore, the detection of a mutated hChaT gene, which would likely lead to an acetylcholine deficiency, would be useful in diagnosing the disclosed cognitive and/or neurological deficiencies. *See*, Specification, page 18, paragraph 0087. Similarly, the ability to detect altered levels of hChaT protein would also be useful in diagnosing the various cognitive and/or neurological deficiencies since the enzyme is responsible for the synthesis of acetylcholine. *Id.* at paragraph 0092.

Applicants note that the specification does, indeed, provide ample guidance for one of ordinary skill in the art to routinely carry out the methods of the claimed invention without undue experimentation. The specification discloses well known sequencing techniques which would be useful for determination a hChaT polynucleotide sequence obtained from a patient's cells, such as from blood, tissue biopsy and autopsy material. For example, the specification discloses that "the detection of a specific DNA sequence may be achieved by methods such as hybridization, RNase protection, chemical cleavage, direct DNA sequencing or the use of restriction enzymes, and Southern blotting of genomic DNA." *See*, Specification, page 18, paragraphs 0087 to 0090. Accordingly, a skilled artisan, after sequencing the hChaT polynucleotide from a patient sample, could readily "determine the differences in the cDNA or genomic sequence between affected

and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease." *Id.* at pages 20-21, paragraph 0100.

The specification, as filed, is also enabling for methods of diagnosing a disorder in a patient by determining altered hChaT protein levels. The specification discloses methods to determine altered levels of hChaT polypeptides in patient samples by comparing the results obtained to standards established from healthy individuals without disorders. *See*, Specification, page 18, paragraph 0092. Furthermore, the specification discloses that "[a]ssays used to detect levels of hChaT protein in a sample derived from a host are well-known to those of skill in the art and include radioimmunoassays, competitive-binding assays, Western Blot analysis, ELISA assays and 'sandwich' assay." *Id. See also* Specification, page 19, paragraphs 0092-0094 describing methods of various protein assays.

Accordingly, the publication by Hersh *et al.* (submitted as Reference D in Applicants' Information Disclosure Statement of August 29, 2003) corroborates Applicants assertion that diagnosing altered levels of hChaT is indeed a useful method for determining the presence or absence of various cognitive and/or neurological deficiencies. Hersh *et al.*, in describing the involvement of an hChaT enzyme in Alzheimer's disease, states that the "progressive loss of ChaT, which results in a decrease in the concentration of the neurotransmitter acetylcholine, has been reported to directly correlate with the memory loss which occurs in this disease." *See* Hersh et al. (1989), page 1, first paragraph. Thus, knowing the correlation of the expression level of ChaT in such cholinergic system disorders as Alzheimer's disease, one of skill in the art would readily appreciate the use of a diagnostic method for ChaT in determining the cognitive and/or neurological deficiencies related to ChaT.

Given the teachings of the specification for making and using assays for determining hChaT mutations and protein levels as well as the *corroborating* publication by Hersh *et al.*, it cannot be said that the invention as claimed is not enabled. Moreover, the skilled artisan, enlightened by the teaching of the present specification and the high level of skill in the art, would be more than capable of routinely making and using the claimed diagnostic methods which merely entail determining a polynucleotide sequence or a level of protein expression. Therefore, in light of the above listed facts, it is clear that the specification as originally filed does indeed enable the diagnostic methods of the

claims. Accordingly, Applicants respectfully request that the rejection of claims 125-144, under 35 U.S.C. § 112, first paragraph, for lack of enablement, be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. The Examiner is invited to call the undersigned if any further action by Applicants would expedite the allowance of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Dated: December 12, 2005

Respectfully submitted,

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